CHAPTER 3: SSB AT MOLECULAR SCALES – PARTIAL AUTOCATALYSIS

3.1 Introduction

In the previously studied model of pure autocatalysis, the broken symmetry state, once achieved remains stable forever. Dynamics in the steady state, arising from say thermal fluctuations, do not take the system out of this symmetry broken state. In many situations, one might desire temporal switching between one broken symmetry state and another - a switching between, say two binary alternatives. A simple and natural way to achieve this is to include a direct or spontaneous formation of the product. In this chapter, we include the effect of spontaneous formation of product, in addition to the autocatalytic reactions studied in the last chapter; we call this partial autocatalysis.
3.2 A Model of partial autocatalysis

Again consider a box containing chemical reactants $A$ and $B$ whose reaction network is shown in Fig. 3.1 – in addition to the linear autocatalysis of Fig. 2.1, there is a spontaneous rate of formation of $R$ & $R^*$, with a rate $k_0$.

Figure 3.1: Partial autocatalysis: $R$ and $R^*$ formed with a spontaneous rate $k_0$, in addition to the linear autocatalysis of the last chapter.

3.3 Mean-field analysis

The mean-field autocatalytic reaction-diffusion equations of Fig. 3.1, is given by

$$\begin{align*}
\partial_t n_A &= -(2k_0 + k_1(n_R + n_{R^*}))n_A n_B + k_2(n_R + n_{R^*}) + D_A \nabla^2 n_A \\
\partial_t n_R &= (k_0 + k_1 n_R)n_A n_B - k_2 n_R + D_R \nabla^2 n_R \\
\partial_t n_{R^*} &= (k_0 + k_1 n_{R^*})n_A n_B - k_2 n_{R^*} + D_{R^*} \nabla^2 n_{R^*}
\end{align*}$$  (3.1)

The rates of reactions $k_1$, $k_0$ and $k_2$ have units of $m^6 s^{-1}$ per mole$^2$, $m^3 s^{-1}$ per mole and $s^{-1}$ respectively.

These equations are again perfectly symmetric. Starting with equal initial concentrations of $R$ and $R^*$ leads to symmetric solution in steady-state – as before the deterministic solution is monostable. We study the effects of stochasticity using the Gillespie algorithm (Section 2.5).
3.4 Symmetry breaking and its restoration: a phase diagram

Our stochastic simulations of the chemical dynamics, show a rich behaviour of steady states and their dynamics, as a function of $k_0 (c_0 \xi^2)$ and the total number of molecules $N = N_A + N_R + N_{R^*}$. We keep all other parameters fixed $- k_1 = 10s^{-1}$, $k_2 = 0.1s^{-1}$. The parameter $k_2$ sets the time scale in the chemical Master equation.

We define the order parameter characterizing the different phases as,

$$\Phi = \frac{N_R - N_{R^*}}{N_R + N_{R^*}}$$

To obtain good statistics for the single-point distribution of $\Phi$, we have collected data over 20 realisations of random number seeds.

For $k_0=0$, the system evolves to one of the broken symmetry states, $+1$ or $-1$, the distribution over several realisations is bimodal.

For small values of $k_0$, starting from any symmetric initial condition, the system reaches one of the broken symmetry states $+1$ or $-1$. However this broken symmetry state is transient, the system makes excursions from this state before switching over to the other broken symmetry state. This process repeats indefinitely (Fig. 3.2 (b) & (c)), the switching time is stochastic and depends on both $k_0$ and $N$. Thus there is no steady state in this strict sense, as soon as $k_0 \neq 0$. Every realisation generates ‘trajectories’ with same statistical properties.

However the switching time increases with decreasing $k_0$. Surprisingly the switching time decreases weakly at first and then more rapidly with increasing $N$! This is presumably because fluctuations which are responsible for the generation of symmetry breaking in these autocatalytic systems die down as
Figure 3.2: Time evolution of order parameter $\Phi$ starting with a symmetric initial condition ($\Phi = 0$): (a) for $k_0 = 0$ the dwell time ($\tau_{\text{dwell}}$) in the symmetry broken phase is infinite (b) as $k_0$ increases for a fixed value of $N$, and (c) as $N$ increases for a fixed value of $k_0$. 
$N$ gets larger. For larger values of $k_0$, the order parameter fluctuates about $\Phi = 0$.

Given the excursions traced out by the late time $\Phi$, we can compute its distribution both over time and over different realisations, Fig. 3.3 (we have checked that the distribution obtained by these two methods is the same). For small $k_0$ (and fixed $N$), the distribution is bimodal at $\pm 1$, which then goes over to a unimodal distribution centered about 0. The same transition from a bimodal to unimodal distribution occurs when $N$ is increased, keeping $k_0$ fixed. Note that at the transition from bimodal to unimodal, the distribution is flat, suggesting that the transition occurs across a critical point.

The typical value (mode) of the distribution $\Phi_t$ can be used as a measure of the excursions between states. Figure 3.4 shows that for a fixed value of $N$, the typical value $\Phi_t$ exhibits a pitchfork bifurcation (47) at the critical point $k_0 = k^*_0$, where $k^*_0 \approx 0.092$ for $N = 110$.

Fig. 3.5 shows the phase diagram in the $k_0 - N$ plane, illustrating the broken symmetry phase when number fluctuations are appreciable and the spontaneous rate of formation $k_0$ is negligible. Upon increasing either or both the parameters ($k_0, N$), the system enters into a mixed phase, where it exhibits transient excursions across the broken symmetry steady states. Further for large enough values of the parameters, the symmetry is restored. The phase transition from the mixed phase to the symmetric phase is continuous.

This study demonstrates that a spontaneous rate of formation of products counteracts the effects of autocatalysis, serving to restore the symmetry spontaneously broken by fluctuations.
Figure 3.3: Probability distribution of the order parameter $\Phi$. There is continuous transition from bimodal to unimodal distribution: (a) as $k_0$ increases for a fixed value of $N$ ($N = 110$) (b) as $N$ increases for a fixed value of $k_0$ ($k_0 = 0.05$).
Figure 3.4: Pitchfork bifurcation of the mode $\Phi_t$ of the distribution $P(\Phi)$ as a function of $k_0$. There is a critical point at $k_0^* \approx 0.092$ for $N = 110$.

3.5 Cellular application(s)

We now discuss a particularly interesting application of this mechanism in the context of intracellular trafficking of cargo.

3.5.1 Molecular segregation and Compartmental identity in the Golgi

In Eukaryotic cells, directed cargo transport across membrane bound organelles is mediated by the dynamical processes such as budding, fission & fusion of membrane bound vesicles. Newly synthesised lipids and proteins are trafficked via the secretary pathway, endoplasmic reticulum($ER \rightarrow Golgi \rightarrow$ plasma membrane($PM$). Many and highly specific molecular machines are involved in the regulation of budding, transport and fusion of cargo vesicles containing these lipids and proteins, which shuttle back and forth from these membrane bound compartments. Thus, while GTPase mediated activation
Figure 3.5: Phase diagram in $k_0 - N$ plane. There is continuous transition from the mixed phase (exhibiting transient excursions) to the symmetric phase.

of coatamer proteins along with a host of other proteins lead to budding, membrane-bound SNARE proteins along with NSF mediate fusion of those budded vesicles on the target compartment. Inspite of such constant flux of material transported across intracellular organelles (section 1.2), how is the compositional identity of organelles preserved?

Ref (6) has addressed this issue with a detailed modeling taking into account the vesicle budding and fusion processes. They have analysed a subnetwork of the secretory trafficking network – focussing on the trafficking between only two compartments. For this, they have considered two types of coatamer proteins, SNAREs, the different types of vesicles budding from ER and Golgi organelles and the sizes of those compartments. This two compartment model was then extended to three compartment model. The two compartment model also accounts for the following processes: (i) effect of inhibitory SNARES (ii) net unidirectional flux of cargo entering compartment 1 and leaving compartment 2 (iii) inhibition of back fusion of vesicles.

The main drawback of this model is that even with this simplification, it is
too detailed, with too many free parameters – as many as 22! It is therefore not reasonably generic and does not provide a qualitative understanding.

Therefore we propose a more minimal model (Fig. 3.6), applying our understanding of the role of partial autocatalysis coupled with antagonism, in order to understand molecular segregation in the golgi cisternae. Our strategy of compartmentalisation takes into account some level of spatial scales.

![Figure 3.6: Minimal model with partial autocatalysis & antagonism for molecular segregation. See text for explanation.](image)

Consider two compartments which are initially identical with equal number of SNARES $A_i, B_i$, $i = 1,2$ in them. Total number of $A$ and $B$ are conserved ($A_1 + A_2 = a, B_1 + B_2 = b$). Transport of $A$ and $B$ between compartments happens with a spontaneous rate $k_0$ and linear autocatalytic rate $k_1$ (eg: $k_1 P(N_{A_2})$, for $A_1 \rightarrow A_2$), additionally there is antagonism exhibited by the other SNARE ($B_2$) in the target compartment where it fuses. Such a minimal model leads to the following phases:

(i) $k_0 = 0$, no antagonism: The two ($A$ & $B$) subnetworks are completely
Figure 3.7: Steady state probability distributions $P_1(A)$ and $P_1(B)$ as a function of $\frac{k_0}{k_1}$: (a) Complete molecular segregation for $\frac{k_0}{k_1} = 1$ (b) increasing the ratio, results in segregation accompanied by vesicular transport for $\frac{k_0}{k_1} = 1.2142$ (c) gets into maturation of organelles for larger values ($\frac{k_0}{k_1} = 1.7$) (d) There is complete mixing for large enough values ($\frac{k_0}{k_1} = 8.5$).
decoupled and hence no phase segregation.

(ii) $k_0 \neq 0$ with antagonism: The simplest coupling term could be antagonism which is a linear function of the opposite type of SNARE (say $B_2$ for $A_1 \rightarrow A_2$) in the target compartment. In order to account for spatial heterogeneity in molecular distribution in a compartment, we assume that the probability of a SNARE enhancing its production via autocatalysis is non-zero, only if its instantaneous concentration is larger than its opponent’s in the target compartment. We apply this assumption consistently to $A$ and $B$ in both the organelles. For $k_0/k_1 = 1$, there is complete segregation halting transport ($j_{12} = j_{21} = 0$); every organelle has a distinct type of SNARE with no remnants of the other SNARE. But if the ratio becomes larger than one, then the compartments still retain their identity but with a non-zero concentration of the other SNARE. Thus it retains vesicular transport across organelles ($j_{12}, j_{21} \neq 0$). Upon further increasing the ratio, the organelle composition switches from one type to the other. This phase can be thought of as a precursor to cisternal maturation (3) – an organelle with a composition (say $\phi_1 \gg 0, \phi_2 \ll 0$) matures, in time, to the opposite ($\phi_1 \ll 0, \phi_2 \gg 0$) type. However to make this identity with cisternal maturation rigorous, one needs to include the flux of particles flowing in and out of the compartments from reservoirs.

When the ratio is large enough, the compartments become identical in their composition and mix completely – restoration of symmetry. Fig. 3.7 shows the variations in the probability distribution of the SNARES $A$ and $B$ upon increasing the ratio $\frac{k_0}{k_1}$.

Thus while very large $k_0$ would result in non-zero current for transport but identical compartments, $k_0/k_1 = 1$ would halt transport reaching complete segregation. Hence it is necessary to maintain $k_0 \neq 0$ and small for optimal
Figure 3.8: Qualitative phase diagram: Phase transition from molecular segregation to complete mixing. Intermediate regime has interesting phases, where there is vesicle transport and maturation of golgi cisternae. Colours of the compartments indicate their composition in the respective phases.

segregation and maintenance of transport across organelles.

Fig. 3.8 summarises the different phases.

We conclude with the following speculation. A continuous phase transition, from a racemic phase to a broken symmetry phase via a critical point suggests that, it has interesting implications in the context of sensitive cellular response. Amplification of weak input signal is achievable, if a system is maintained closer to the critical point. We speculate that such a heightened sensitivity at criticality might be a common feature in many cellular contexts such as – (a) the sensitive detection of as few as 3 agonists in a pool of thousands of endogenous pMHC molecules by a T-cell, triggering downstream signaling (b) self-tuned criticality in spontaneous oscillations (48) of hair bundles in auditory cells.